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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,866	02/28/2006	Borek Zaludek	J187-030 US	9742

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,866	ZALUDEK ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response filed on **7/24/08** presents remarks and arguments to the office action mailed on **4/29/08**. Applicant's request for reconsideration of the rejection of claims in the last office action has been considered.

Applicant's arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of Claims

Claims 1-3 are pending in this office action. Claims 4-5 are cancelled.

Response to argument under 103 rejection:

Applicant argues by posing several questions.

Applicant argues whether the ratio 1:4.5 of Dexter would be helpful for the person skilled in the art working to develop a freeze-dried composition only comprising oxaliplatin and alcoholic sugar?

In response, yes, because Bouloumie teaches that the concentration of mannitol is 9 mg (see col. 10, lines 10-11) and the concentration of the drug oxaliplatin is 1.18. Accordingly, the ratio of oxaliplatin to mannitol is 1:7.6. Thus, the ratio of Dexter is

within experimental and the purview of the skilled artisan and hence, the skilled artisan could optimize the optimum working range. Regarding claims 10-11, 18-19 and 28-29 with particular concentrations and ratios, Dexter teaches (For example, that 100 mg of oxaliplatin is used with 450 mg of lactose, wherein the ratio is 1:4.5) which is within the claimed invention. Note, as explained in the last office action that stated substituting lactose for mannitol would have been obvious even though Applicant correctly states lactose is not a non-alcoholic sugar, however, because the prior art had employed mannitol prior to Applicants' invention (see Bouloumie), substituting the lactose in Dexter with the mannitol in Bouloumie would have been obvious to one of ordinary skill in the art. Also it would have been "obvious to try" by substituting lactose to mannitol in the ratios given since both agents (mannitol and lactose) have been employed in the prior art.

It is the Examiners view that once the concept is known or available, one of ordinary skill in the art would be motivated to find the optimum working range *supra*. Also it has been held that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See In re Aller, 220 F.2d 454 105 USPQ 233,235 (CCPA 1955).

Applicant further argues that if a person skilled in the art working to develop a freeze-dried composition only comprising oxaliplatin and alcoholic sugar find helpful instruction from Boulomie's freeze-dried composition comprising oxaliplatin, the alcohol sugar mannitol and the amino acid alanine?

In response, yes, because Bouloumie teaches oxaliplatin can be freeze-dried with mannitol wherein the concentration of mannitol is 9 mg and the concentration of the

oxaliplatin is 1.18. Both Bouloumie and Dexter employed a sugar in the freeze-drying procedure of oxaliplatin. Bouloumie in the reference teaches the advantages of employing mannitol in a freeze drying that mannitol makes it possible to maintain the solid and the rigid structure of the volume of the freeze-dried product and also makes it possible to adjust the isotonicity of the reconstituted solution. As explained in the last office action that stated substituting lactose for mannitol would have been obvious even though Applicant correctly states lactose is not a non-alcoholic sugar, however, because the prior art had employed mannitol prior to Applicants' invention (see Bouloumie), substituting the lactose in Dexter with the mannitol in Bouloumie would have been obvious to one of ordinary skill in the art. Also it would have been "obvious to try" by substituting lactose to mannitol in the ratios given since both agents (mannitol and lactose) have been employed in the prior art.

Question 3: Could the person skilled in the art working to develop a freeze-dried composition only comprising oxaliplatin and alcoholic sugar be aided by the combination of Boulomie and Dexter.

Yes. See above.

Question 4: Does Ibrahim include helpful instructions leading to the weight ratio of oxaliplatin to the alcoholic sugar of from 1:3 to 1:7 as set forth in claim 1?

Yes, see above. To summarize all the questions the combination of references would have made it obvious to arrive at the claimed invention because the test for obviousness is not whether the features of a secondary references may be bodily

incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

With regard to the statement, "*The cited references disclose a freeze-dried composition having a mannitol (alcoholic sugar) with oxaliplatin in a ration of 1:4.5".* Examiner has withdrawn the statement and has replaced it with lactose. The Examiner would like to thank Applicant for bringing that to attention. The rejection has been modified below to correct typo.

Claim Rejections - 35 USC § 103(clarification made to the rejection below, no new citations added)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ibrahim et al. WO 94/12193 in view Bouloumie et al., US 6,284,277 and further in view of Dexter et al., US 6,063,780.

The claims recite a pharmaceutical composition prepared by freeze drying in a vacuo, containing oxaliplatin as the active component and a pharmaceutically acceptable carrier, characterized in that the carrier is at least one alcoholic sugar of non-animal origin, the weight ratio of oxaliplatin to the alcoholic sugar of non-animal origin or alcoholic sugars of non-animal origin being 1:3 to 1:7.

Ibrahim et al, teach a freeze –dried composition comprising oxaliplatin and a mannitol, see abstract and page 7 example 2. The reference also teaches that the composition is placed (60 ml) in a vial (falcon). It is understood that the size of the container is not taught, however, 60 ml is equated to occupying 60% of the capacity of a vial, cooled and freeze dried at temperatures of -50. See pages 9, lines 9-16. (Thus

interpreted as prepared by freeze-drying). The reference fails to teach the ratio of oxaliplatinum and mannitol.

Boulomie et al is introduced for its teaching of a ratio of 1:7.6 of oxaliplatinum and mannitol.

Boulomie et al. teach a freeze-dried pharmaceutical formulation, wherein the active agent is oxaliplatin. See col. 6, lines 58-60 and col. 7, line 7. The reference also teaches that the active agent is freeze-dried in a formulation of mannitol (an alcoholic sugar). See col. 10, lines 10-30 as required by instant claims 1-3 and 4(in part). Bouloumie teaches that the concentration of mannitol is 9 mg and the concentration of the drug is 1.18, accordingly the ratio is 1:7.6; see col. 10, lines 10-15.

Dexter et al. teach administering an effective amount of a platinum complex compound (see abstract) in a freeze-dried formulation in a concentration of 1:4.5 of the lactose. See col. 5, lines 60-63. (For example, 100 mg of oxaliplatin is used with 450 mg of lactose, then the ratio is 1:4.5), which is within the claim limitation of claims 1 and 4.

One of ordinary skill in the art would have been motivated to combine the cited prior art of Ibrahim et al. with Boulomie because freeze dried oxaliplatin have been taught in the prior art of record. The cited references disclose a freeze-dried composition having a mannitol (alcoholic sugar) with oxaliplatin.

With regards to the ratio, it is the Examiners position that once the concept is known or available, one of ordinary skill in the art would be motivated to find the optimum working range. Also it has been held that where the general conditions of a

claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine. See In re Aller, 220 F.2d 454 105 USPQ 233,235 (CCPA 1955).

It would have been obvious to have made a freeze-dried composition that comprises oxaliplatin and mannitol because such is known in the art. As with the concentration it is within the purview of the artisan to optimize.

Maintained Claim Rejections - 35 USC § 103

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bouloumie et al., US 6,284,277 in view of Dexter et al., US 6,063,780.

Boulomie et al. teach a freeze-dried pharmaceutical formulation, wherein the active agent is oxaliplatin. See col6, lines 58-60 and col. 7, line 7. The reference also teaches the active agent is freeze-dried in a formulation of mannitol (an alcoholic sugar). See col. 10, lines 10-30 as required by instant claims 1-3 and 4(in part). As to instant claim 5, oxaliplatin is a known anticancer agent and belongs to the group of platinum drug derivatives; therefore one of ordinary skill in the art would have been motivated to use oxaliplatin for the treatment of cancer.

The above reference, however, fail to teach the range of oxaliplatin and the non-alcoholic sugar.

Dexter et al. teach administering an effective amount of a platinum complex compound (see abstract) in a freeze-dried formulation in a concentration of 1:4.5 of the alcoholic sugar lactose. See col. 5, lines 60-63. (For example, 100 mg of oxaliplatin is

used with 450 mg of lactose, then the ratio is 1:4.5), which is within the claim limitation of claim 1 and 2. The formulation is used for the treatment of tumors see col. 6, lines 13+. It is noted that the reference teaches lactose instead of mannitol.

However, one of ordinary skill in the art would have been motivate to substitute the alcoholic sugar lactose with that of mannitol and freeze –dry the formulation in a concentration recited by Dexter et al. for the administration to tumor patients as taught by Dexter et al. See col. 6, lines 13+.

As to the procedure on how to freeze-dry the formulation, one of ordinary skill in the art would follow the manual procedure for freeze-drying based on the instrument used. It is common knowledge to refrigerate or place on ice the composition for freeze-drying before attempting freeze-drying. As evidence by Laboratory procedures for microorganisms, the vials containing the active agent is place at –20 ° C before the freeze drying procedure. Bouloumie et al. teach that the rate of freezing in a vacuum is -2° C/min. University of Cambridge discloses that there are lots of different ways of lyophilizing or removing water, and the process chosen to formulate a particular drug will depend on the intended delivery method as well as the stability of the substance as evidence by.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/S. V. G./
Examiner, Art Unit 1618
10/29/08